Attorney Docket No.: **ISPH-0591**
Inventors: **Crooke and Graham**
Serial No.: **09/917,963**
Filing Date: **July 30, 2001**
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REMARKS

Claims 1, 2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 16-20 have been canceled. Claims 1, 11 and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner suggests that the specification, while being enabling for inhibition of MTP in cells in culture via antisense compounds, is not enabling for *in vivo* uses of the claimed antisense compounds. The Examiner cites several articles on the technology of antisense to support the position regarding extrapolation to *in vivo* and pharmaceutical uses. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's suggestion that the cited references support the position that application of antisense *in vivo* as a pharmaceutical is unpredictable.

The Examiner has pointed to three articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including antisense technology, and its use in human disease. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

The paper by Agrawal (1996) is an older paper on the development of antisense compounds. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 and canceled claims 16-20, with Applicants reserving the right to file a continuing application directed to this subject matter. Therefore, withdrawal of the rejection is requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wetterau et al. (US Patent 5,595,872) Beissen et al. (2000), Bennett et al. (US Patent 5,998,148), and Baracchini et al. (US Patent 5,801,154). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to make antisense oligonucleotides as claimed because Wetterau et al. and Beissen et al. disclose the use of antisense oligonucleotides to inhibit expression of microsomal triglyceride transfer protein in cells, while Baracchini et al. and Bennett et al. teach the claimed modifications. The Examiner suggests one would have been

motivated to make the claimed invention since the prior art has taught the desirability of using antisense to inhibit microsomal triglyceride transfer protein and microsomal triglyceride transfer protein has been linked to disease. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended claim 1, and by dependency claims 2-20, to identify specific regions within the sequence of microsomal triglyceride transfer protein of SEQ ID NO: 3 that are to be targeted by antisense compounds. These regions are taught in the specification as filed at pages 85-87.

US Patent 5,595,872 (Wetterau et al.) discloses nucleic acid sequences encoding the high molecular weight subunit of microsomal triglyceride transfer protein as well as expression vectors containing said nucleic acids. Additionally claimed are nucleotide sequences fully complementary to the microsomal triglyceride transfer protein sequences. Generally described are methods using antisense for the reduction of microsomal triglyceride transfer protein expression in cells. However, nowhere does this patent teach or suggest antisense compounds targeted to regions within nucleic acid molecules of SEQ ID NO: 3 encoding microsomal triglyceride transfer protein.

Beissen et al. (2000) is an abstract only. This abstract discloses the use of antisense compounds targeted to mouse microsomal triglyceride transfer protein for inhibition of gene expression and as potential hypocholesterolemic agents. Nowhere does this abstract teach or suggest use of antisense compounds targeted to human microsomal triglyceride transfer protein of SEQ ID NO: 3.

Bennett et al. (US Patent 5,998,148) disclose the use of antisense compounds to inhibit expression of human microtubule-associated protein 4. Nowhere does this patent teach or suggest antisense compounds targeted to specific regions of human microsomal triglyceride transfer protein of SEQ ID NO: 3.

Baracchini et al. (US Patent 5,801,154) disclose teaches methods of modifying antisense oligonucleotides to enhance activity. However, nowhere does this patent teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to human microsomal triglyceride transfer protein of SEQ ID NO: 3 as claimed, or any region of human microsomal triglyceride transfer protein of SEQ ID NO: 3.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in

the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to specific regions of human microsomal triglyceride transfer protein of SEQ ID NO: 3, and thus cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 16-20 have been canceled.

Claims 1, 11 and 15 have been amended as follows:

1. (twice amended) A compound 8 to 50 nucleobases in length targeted to a 5'-untranslated region, a start codon region, a coding region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule of SEQ ID NO: 3 encoding human microsomal triglyceride transfer protein ~~(SEQ ID NO: 3)~~, wherein said compound specifically hybridizes with one of said regions and inhibits the expression of human microsomal triglyceride transfer protein.

11. (amended) A compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule of SEQ ID NO: 3 encoding human microsomal triglyceride transfer protein, wherein said active site is listed in Table 1.

15. (amended) A method of inhibiting the expression of human microsomal triglyceride transfer protein in cells or tissues comprising contacting said cells or tissues *in vitro* with the

compound of claim 1 so that expression of human microsomal triglyceride transfer protein is inhibited.